UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C.
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
08/366,083	12/29/1994	JOEL L. POMERANTZ	APBI-P01-022	6870

28120 7590 10/02/2002

ROPES & GRAY
ONE INTERNATIONAL PLACE
BOSTON, MA 02110-2624

EXAMINER	
MCKELVEY, TERRY ALAN	
ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 10/02/2002

41

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)
	08/366,083	POMERANTZ ET AL
	Examiner	**Art Unit**
	Terry Mckelvey	1636

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 July 2002*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-21,24,27-30,34,36,40-70,72-98* is/are pending in the application.

4a) Of the above claim(s) *1-21,24,27-30,34 and 36* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *40-70-72-98* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____
4) ☐ Interview Summary (PTO-413) Paper No(s) _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 7/9/02 has been entered.

Election/Restriction

Claims 1-21, 24, 27-30, 34, and 36 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b) as being drawn to a non-elected invention. Election was made **without** traverse in Paper No. 12, filed 3/19/98.

This application contains claims 1-21, 24, 27-30, 34, and 36 drawn to an invention nonelected with traverse in Paper No. 12. The complete response to the previous final rejection should have included cancellation of the nonelected claims or other appropriate action. Neither action was taken. This requirement is maintained.

Claim Objections

Claim 92 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. This is a new objection.

In the instant case, claim 92 improperly depends on canceled claim 71, and thus fails to limit the subject matter of a previous claim because the previous claim no longer is pending.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) do not apply to the examination of this application as the application being examined was not (1) filed on or after November 29, 2000, or (2) voluntarily published under 35 U.S.C. 122(b). Therefore, this application is examined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

Claims 40, 55-59, 61, 65, 72-76, 80, 83-88, 90, 93-94, and 96-97 are rejected under 35 U.S.C. 102(e) as being anticipated by Barbas et al (U.S. Patent No. 6,242,568). This is a new rejection.

Barbas et al teach a nucleic acid encoding two or more heterologous zinc finger modules that bind to a cellular nucleotide sequence and modulate the function of the cellular nucleotide sequence (columns 3-4; throughout the reference and claims). Examples of known zinc finger-nucleotide binding proteins that can be truncated, expanded, and/or mutagenized according to the present invention in order to inhibit the function of a cellular sequence containing a zinc finger-nucleotide binding motif includes TFIIIA and zif268. Others are known in the art (column 7). For obtaining zinc finger derived DNA binding polypeptides, the synthesis of DNA sequences is

frequently the method of choice when the entire sequence of amino acid residues of the desired polypeptide product is known (column 9). This reference teaches placement of the nucleic acid encoding the proteins containing the chimeric zinc finger domains into vectors for expression in eukaryotic cells, under the control of a promoter sequence (column 16). Barbas et al also teach that the zinc fingers may be modified to recognize a different sequence, and fused to other proteins which are capable of forming heterodimers and contain dimerization domains. Activation domains may also be incorporated to produce activators of transcription, which then allow for specific activation or repression of transcription (columns 27-28). A particular example of this type of construct is taught (column 29).

Claims 40, 55-57, 65, 72, 90, 94, and 97 are rejected under 35 U.S.C. 102(b) as being anticipated by Desjarlais et al. This is a new rejection.

Desjarlais et al teach designing three zinc-finger proteins with different DNA binding specificities. The design strategy combines a consensus zinc-finger framework sequence with previously characterized recognition regions such that the specificity of each protein is predictable. A protein is taught

that has three different zinc finger domains, each recognizing a different 3 nucleotide sequence component of the final composite site (abstract). The genes encoding the proteins are also taught, as are expression vectors which contain a promoter operatively linked to the gene encoding the proteins (Materials and Methods section).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35

U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claims 40-70, 72, 89-92, 94-95, and 97 are rejected under 35 U.S.C. 103(a) as being unpatentable over Park et al (AW2) in view of Mitchel et al (S), Harrison (T) and Schultz (U). This rejection is maintained for reasons of record set forth in Paper No. 23, mailed 11/9/98, Paper No. 27, mailed 8/4/99, Paper No. 33, mailed 9/21/00, and Paper No. 37, mailed 6/4/01, and repeated below. Applicants did not present any new arguments with the RCE filed 7/9/02. The response to applicants' last arguments filed 3/23/01 have been repeated below. Applicants' arguments remain unpersuasive.

Park et al teach a general strategy for designing proteins to recognize specific DNA-binding sites: this strategy is to select segments of proteins, each of which recognizes particular DNA segments and to stitch these segments together via a short peptide with a cysteine crosslink in a way compatible with each peptide being able to bind to its own DNA segment. This technique creates a protein that recognizes the composite site (page 9094, column 1). This reference also teaches that use of the Gly-Gly-Cys linker is not essential in the design, that the cysteine can be replaced and a continuous approximately 70 amino-acid protein that should recognize a predictable site can be made (page 9095, column 2). The design is not limited to v-Jun. Any protein or other molecule that recognizes a specific

DNA sequence by binding along the major groove could be a candidate. Many such cases are now known so that we already have a collection of available partial-binding sites that could be combined to form composite target-binding sites for designing binding proteins. Of course, the segments of these proteins should be designed so that the intramolecular interactions are not so strong as to compete with binding to the DNA (pages 9095-9096). Park et al also teach that the strategy is not limited to two arms and that they could have stitched together three, four, or more arms with appropriate linkers to design proteins that would recognize DNA sequences with 15, 20, or 25 bp (page 9095, column 2).

Park et al do not teach to specifically use the DNA-binding domains from distinct families of nucleic acid binding domains, use of specific types of domains such as zinc-finger domains.

Mitchell et al teach that different DNA binding transcription factors are composed of a surprising variety of usually separable DNA binding and transcriptional activation domains (page 372, column 2). This reference teaches zinc-finger domains, homeodomains, helix-turn-helix domains, steroid hormone receptor domains, leucine zipper domains, etc (pages 372-373). Various types of separable activation domains are also taught: acidic domains that can form an amphipathic alpha-helical structure, glutamine-rich domain, and proline-rich domain (pages 373-375).

Harrison teaches that many DNA-binding proteins recognize specific sites through small, discrete domains and that these domains can be interchanged between proteins, showing that they are independent folded units. Many different DNA-binding domains are taught, including HTH, homeodomains, different types of zinc-finger domains, steroid receptor DA binding domains, etc. Representative proteins having the domains, such as Zif268, etc are also taught and referenced (page 715).

Schultz teaches that enzymes can be created by adding or replacing entire binding or catalytic domains to generate hybrid enzymes with novel specificities. Selective fusion of nucleic acid-specific binding domains may produce sequence-specific DNA or RNA cleaving enzymes (page 431, column 1). This reference teaches that tailor-made enzymes have applications in chemistry, biology and medicine.

It would have been obvious to one of skill in the art at the time the invention was made to use the various DNA binding domains, activation domains, and cleavage domains, including heterologous ones, taught by Mitchell et al, Harrison, and Schultz in the general strategy for designing proteins to recognize specific DNA-binding sites taught by Park et al because Park et al teach that it is within the ordinary skill in the art to stitch the DNA binding domains together from any proteins that recognize a specific DNA sequence by binding along the major groove, to recognize a composite site and Mitchell et

al, Harrison, and Schultz teach such domains that can be functionally separated and recombined with other domains. One would have been motivated to do so for the expected benefit of creating a protein that recognizes the composite site, thereby increasing the specificity of the chimeric protein, as taught by Park et al, and creating hybrid enzymes with novel specificities that have applications in chemistry, biology and medicine as taught by Schultz. Absent evidence to the contrary, there would have been a reasonable expectation of success that the domains taught by Mitchell et al and Harrison could be combined with each other to create a protein that recognizes a composite binding site as taught by Parks et al.

With regard to making a nucleic acid and vector comprising the nucleic acid which encodes the chimeric protein, it would have been obvious to do so because Parks et al teach that a continuous approximately 70 amino-acid protein that should recognize a predictable site can be made, instead of using a cysteine linker, and thus it would have been obvious to make a nucleic acid that encodes this protein and place the nucleic acid in a vector to express the protein, because such a way of making a mutated, recombinant protein is and was well known in the art.

With regard to the use of any specific domain or combinations of domains recited in the claims, it would have been obvious to make any of the recited combinations because the

recited domains are all taught in the cited references or are and were well known in the art, and Parks et al teach that any combination of domains can be used, which would include heterologous ones.

With regard to the inclusion of an activation domain in the chimeric protein, it would have been obvious to do so because the cited references teach that the activation domain are separate from the DNA binding domains and thus can be included. One would have been motivated to do so for the expected benefit of making a transcriptional activation protein that binds to a more specific composite site, as taught by Parks et al.

With regard to separating the domains by one or more amino acids in the chimeric protein, it would have been obvious to do so because Parks et al teach that the domains can be separated by a linker.

With regard to including an additional (third) nucleic acid binding domain, it would have been obvious because Park et al teach that more domains can be added, resulting in binding to a larger composite DNA binding site.

Response to Arguments

The applicant argues that it is plain that in its broadest sense Park et al is still limited to the use of cross-linking agents to generate chimeric DNA binding proteins from discontinuous polypeptide fragments because this reference

teaches covalent stitching together of DNA-binding proteins to form a cysteine-crosslinked composite protein, and that the disclosure may be a general strategy for designing cysteine-crosslinked protein composites, but it does not in any way disclose the possibility of or suggest the desirability of designing making or using nucleic acids. This argument is not persuasive for the following reasons. First, the applicant is completely ignoring a part of the teaching of Park et al upon which the instant rejection rests which was clearly set forth above and in the previous Office Actions. Park et al specifically teaches that cysteine crosslinking is not essential for the design and that a continuous protein that recognizes a predictable site can be made: "Summarizing, we have designed a protein (stitched together from segments derived from the natural protein) to recognize a specific DNA-binding site, and we have established specific binding of the designed protein to this site. Note that use of the Gly-Gly-Cys linker is not essential in the design. We could just as well replace the cysteine and make a continuous (about) 70-amino acid protein that should recognize a predictable site (14)." (page 9095, column 2, beginning of the first full paragraph). This passage clearly shows that Park et al contemplated more than just cysteine-crosslinked proteins that are designed to bind to a specific DNA sequence. This reference explicitly states that the protein can be designed as a continuous protein. Second,

although Park et al does not specifically teach that the continuous about 70 amino acid protein that the reference refers to may be made from a nucleic acid sequence which encodes it, the instant rejection does not rely upon Park et al alone to teach that a nucleic acid sequence should be made that encodes that type of protein. Making a mutated, recombinant protein by making a nucleic acid sequence that encodes the protein and placing the nucleic acid in a vector to express the protein is and was extremely well known in the art. This technology has been at the very heart of the entire biotechnology industry for decades and clearly is obvious to one of ordinary skill in the art! Once it is suggested to one of ordinary skill in the art that a protein be made, it is immediately very obvious to make a nucleic acid sequence encoding the protein and express it from a vector. The applicant has not challenged this specific part of the obviousness argument, that since Park et al teaches making the continuous protein that binds a specific DNA sequence, it would have been obvious to make a nucleic acid sequence encoding the protein and expressing it. However, as further evidence that this is and was very well known, one merely needs to look to the teachings of Gossen et al which is a part of the rejection under 103(a) of claims 40-70 and 72-98 (repeated below), which teaches a nucleotide molecule coding for a chimeric transactivator fusion protein. This reference clearly

teaches expressing chimeric transcription factor proteins from nucleic acid sequences encoding them.

The applicant also argues that the Examiner fails to demonstrate how Park et al bridges the gap between the claimed invention and the deficiencies which the Examiner admits for the remaining references, and that absent a suggestion for the asserted combination in any of the references themselves, the combination of these references is itself legally impressible with respect to maintaining a rejection for obviousness. This argument is not persuasive because what makes the combination of cited references obvious was clearly set forth in the previous Office Actions and repeated in the instant Office Action. How the remaining references (absent Park et al) and what is and was well known in the art remedy deficiencies of Park et al is clearly set forth in specific detail not addressed by the applicant in his instant argument. The applicant has not addressed the particulars of the step by step basis for obviousness that was set forth by pointing out the specific deficiencies of one or more parts of the obviousness argument/rejection. The applicant merely states that the Examiner has failed to demonstrate obviousness. This type of argument, which lacks arguments drawn to why particular parts of the obviousness rejection are deficient, is not persuasive. Instead of repeating the rejections which have already been set forth in their entirety, the applicant is directed to the

rejections themselves which has all pertinent parts of the Graham v. Deere analysis clearly set forth.

Therefore, in light of all available evidence, including the rejection set forth above and in the previous Office Actions, the applicant's arguments, and the arguments set forth above and in the previous Office Actions, the claimed invention is still considered to have been obvious, and the rejection of the claims under 35 USC 103(a) is properly maintained.

Claims 40-70 and 72-98 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ladner et al (U.S. Patent No. 5,198,346) in view of Park et al (AW2), Mitchel et al (S), Harrison (T) and Schultz (U). This is a new rejection.

Ladner et al teach generation and selection of novel DNA-binding proteins obtained by variegation of genes encoding known binding proteins and selection for proteins binding the desired target DNA sequence. Heterooligomeric proteins which bind to a target DNA sequence which need not be palindromic are obtained by a variety of methods, e.g. variegation to obtain proteins binding symmetrized forms of the half-targets and heterodimerization to obtain a protein binding the entire asymmetric target (abstract). This reference teaches that in one embodiment, a gene is constructed that encodes, as a single polypeptide chain, the two DNA binding domains of a naturally-occurring dimeric repressor, joined by a polypeptide linker that holds the two binding domains

in the necessary spatial relationship for binding to an operator (column 12). To obtain a repressor for an arbitrary 17-mer operator, one would find the 5-mer sequence of a left arm in the dictionary (of DNA-binding domains listed by recognition sequence), ignore the sequence and composition of the next 7 bases, find the 5-mer sequence of a right arm in the dictionary, and use the corresponding recognition helix sequence in the second DNA-binding domain of the pseudo-dimer (column 13). Various strategies of linking two different DNA binding domains together into the same protein encoded by a nucleic acid is taught (columns 41-43). The selection of the starting DNA binding domains is taught, including use of helix-turn-helix domains, series of linked small domains such as zinc finger domains (columns 51-55). Use of DNA restriction enzymes and other DNA modifying enzymes which have palindromic or asymmetric recognition from a single polypeptide chain also provide reasonable starting points to generate DNA binding proteins (column 57). This reference teaches that any protein or polypeptide which binds DNA may be used as an initial DNA-binding protein; that the present method is not limited to repressor proteins, but rather includes other regulatory proteins as well as DNA-binding enzymes such as polymerases and nucleases (column 61). Many different proteins having different DNA binding domain types are taught as the starting point for the DNA binding domains (claim 5, for example). Vectors comprising the nucleic

acids encoding the chimeric DNA binding proteins operatively linked to promoters for expression in eukaryotic cells and cells comprising the vectors are also taught, as is the use of the chimeric protein for modulating expression of a gene in a cell comprising modulating expression of the chimeric protein in a cell which includes a gene operably linked to the composite binding site (columns 247-252).

Ladner et al do not teach to specifically use of all of the specific recited combinations of the DNA-binding domains from the distinct families of nucleic acid binding domains, such as specifically including a zinc finger motif or homeodomain as one of the two DNA binding domains.

Park et al teach a general strategy for designing proteins to recognize specific DNA-binding sites: this strategy is to select segments of proteins, each of which recognizes particular DNA segments and to stitch these segments together via a short peptide with a cysteine crosslink in a way compatible with each peptide being able to bind to its own DNA segment. This technique creates a protein that recognizes the composite site (page 9094, column 1). This reference also teaches that use of the Gly-Gly-Cys linker is not essential in the design, that the cysteine can be replaced and a continuous approximately 70 amino-acid protein that should recognize a predictable site can be made (page 9095, column 2). The design is not limited to v-Jun. Any protein or other molecule that recognizes a specific

DNA sequence by binding along the major groove could be a candidate. Many such cases are now known so that we already have a collection of available partial-binding sites that could be combined to form composite target-binding sites for designing binding proteins. Of course, the segments of these proteins should be designed so that the intramolecular interactions are not so strong as to compete with binding to the DNA (pages 9095-9096). Park et al also teach that the strategy is not limited to two arms and that they could have stitched together three, four, or more arms with appropriate linkers to design proteins that would recognize DNA sequences with 15, 20, or 25 bp (page 9095, column 2).

Mitchell et al teach that different DNA binding transcription factors are composed of a surprising variety of usually separable DNA binding and transcriptional activation domains (page 372, column 2). This reference teaches zinc-finger domains, homeodomains, helix-turn-helix domains, steroid hormone receptor domains, leucine zipper domains, etc (pages 372-373). Various types of separable activation domains are also taught: acidic domains that can form an amphipathic alpha-helical structure, glutamine-rich domain, and proline-rich domain (pages 373-375).

Harrison teaches that many DNA-binding proteins recognize specific sites through small, discrete domains and that these domains can be interchanged between proteins, showing that they

are independent folded units. Many different DNA-binding domains are taught, including HTH, homeodomains, different types of zinc-finger domains, steroid receptor DA binding domains, etc. Representative proteins having the domains, such as Zif268, etc are also taught and referenced (page 715).

Schultz teaches that enzymes can be created by adding or replacing entire binding or catalytic domains to generate hybrid enzymes with novel specificities. Selective fusion of nucleic acid-specific binding domains may produce sequence-specific DNA or RNA cleaving enzymes (page 431, column 1). This reference teaches that tailor-made enzymes have applications in chemistry, biology and medicine.

It would have been obvious to one of skill in the art at the time the invention was made to use the various DNA binding domains, activation domains, and cleavage domains, including heterologous ones, taught by Ladner et al, Mitchell et al, Harrison, and Schultz in the general strategy for designing proteins to recognize specific DNA-binding sites taught by Ladner et al and Park et al because Ladner et al and Park et al teach that it is within the ordinary skill in the art to stitch the DNA binding domains together from any proteins that recognize a specific DNA sequence, to recognize a composite site and Ladner et al, Mitchell et al, Harrison, and Schultz teach such domains that can be functionally separated and recombined with other domains. It would have been further obvious to make

the nucleic acid which encodes the protein comprising the two or more DNA binding domains and other domains because Ladner et al specifically teaches construction of these nucleic acids and placement of the nucleic acids into vectors and cells.

One would have been motivated to do so for the expected benefit of creating a nucleic acid, etc, encoding a protein that recognizes the composite site, thereby increasing the specificity of the chimeric protein, as taught by Ladner et al and Park et al, and creating hybrid enzymes with novel specificities that have applications in chemistry, biology and medicine as taught by Schultz. Based upon the teachings of the cited references, the high skill in the art, and absent evidence to the contrary, there would have been a reasonable expectation of success that the domains taught by Ladner et al, Mitchell et al and Harrison could be combined with each other to create a protein that recognizes a composite binding site as taught by Ladner et al and Parks et al, including those which specifically have either a zinc finger domain or homeodomain as one of the two DNA binding domains in the chimeric protein.

With regard to the use of any specific domain or combinations of domains recited in the claims, such as specifically including a zinc finger domain or a homeodomain, it would have been obvious to make any of the recited combinations because the recited domains (especially zinc finger domains and homeodomains, for example) are all taught in the cited

references or are and were well known in the art, and Ladner et al and Parks et al teach that any combination of domains can be used, which would include heterologous ones.

With regard to the inclusion of an activation or repressor domain in the chimeric protein, it would have been obvious to do so because the cited references teach that the activation and repressor domains are separate from the DNA binding domains and thus can be included. One would have been motivated to do so for the expected benefit of making a transcriptional activation protein that binds to a more specific composite site, as taught by Ladner et al and Parks et al.

With regard to separating the domains by one or more amino acids in the chimeric protein, it would have been obvious to do so because Ladner et al and Parks et al both teach that the domains can be separated by a linker.

With regard to including an additional (third) nucleic acid binding domain, it would have been obvious because Ladner et al and Park et al teach that more domains can be added, resulting in binding to a larger composite DNA binding site.

Claims 40-70 and 72-98 are rejected under 35 U.S.C. 103(a) as being unpatentable over Park et al (AW2), Mitchel et al (S), Harrison (T) and Schultz (U) as applied to claims 40-70, 72, 89-92, 94-95, and 97 above, and further in view of Gossen et al (A). This rejection is maintained for reasons of record set

forth in Paper No. 23, mailed 11/9/98, Paper No. 27, mailed 8/4/99, Paper No. 33, mailed 9/21/00, and Paper No. 37, mailed 6/4/01, and repeated below. Applicants did not present any new arguments with the RCE filed 7/9/02. The response to applicants' last arguments filed 3/23/01 have been repeated below. Applicants' arguments remain unpersuasive.

The teachings of Park et al (AW2), Mitchel et al (S), Harrison (T) and Schultz (U) are cited above and applied as before. These references do not specifically teach placing the nucleic acid encoding the chimeric protein into a vector in which the expression of the chimeric protein is under the control of a promoter permitting gene expression in eukaryotic cells, a kit comprising the nucleic acid encoding the chimeric protein and a gene operably linked to the composite binding site, use of the chimeric protein for modulating expression of a gene in a cell comprising modulating expression of the chimeric protein in a cell which includes a gene operably linked to the composite binding site, and a method of making a cell for use in the claimed expression method.

Gossen et al teach a nucleotide molecule coding for a chimeric transactivator fusion protein comprising a DNA binding domain (tet repressor binding domain) and a transactivation domain (such as VP16 of HSV). A negative system, comprising a repressor domain, is also taught (column 2). A second nucleic acid is taught coding for a heterologous protein which is

operably linked to a tet operator (the binding site for the DNA binding domain). A method to regulate gene expression by cultivating the eukaryotic cell comprising the nucleic acid vectors in a medium comprising tet is also taught, as is a kit comprising the nucleic acids (abstract; columns 1-3). A method of making such eukaryotic cells by transfecting the nucleic acids into the cells is taught (columns 3, 9). This reference also teaches that it is desired to create regulatory systems that do not rely on endogenous control elements (column 1).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to form a transcriptional regulatory system from the DNA encoding a chimeric transactivation protein made obvious by the teachings of Park et al (AW2), Mitchel et al (S), Harrison (T) and Schultz (U), using the method taught by Gossen et al because Gossen et al teach that it is within the ordinary skill in the art to make a nucleic acid vector that encodes a chimeric transactivator fusion protein (under the control of a promoter active in eukaryotic cells), make a nucleic acid encoding a heterologous protein operably linked to a regulator binding site that the chimeric protein binds to, place the nucleic acids in a eukaryotic cell, regulate the expression of the chimeric protein, thereby regulating expression of the heterologous protein, and the other cited references teach a chimeric fusion transactivator protein that could be used to regulate the

expression of genes in a similar fashion as that taught by Gossen et al. One would have been motivated to do so for the expected benefit of making regulatory systems that do not rely on endogenous control elements, the desirability of which is taught by Gossen et al. Absent evidence to the contrary, there would have been a reasonable expectation of success that the chimeric protein encoding DNA taught by the other cited references could be used to make a new, non-endogenous element regulatory system using the teachings of Gossen et al.

Response to Arguments

The applicant's arguments as they apply to the instant rejection were addressed above and all counter-arguments apply equally to this rejection and thus the instant rejection under 35 USC 103(a) is maintained for the same reasons as the rejection set forth above.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground

provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 40, 45, 50, 57-59, 61, 63, 66, 68-70, 72-78, 80, 83-91, and 93-98 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-11, 17, 21, 23, and 44-60 of U.S. Patent No. 6,326,166. This is a new rejection.

An obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985). Although the conflicting claims are not identical, they are not patentably distinct from each other because claims 40, 45, 50, 57-59, 61, 63, 66, 68-70, 72-78, 80, 83-91, and 93-98 are generic to all that is recited in claims 1-11, 17, 21, 23, and 44-60 of '166. That is, claims 1-11, 17, 21, 23, and 44-60 of '166 falls entirely within the scope of claims 40, 45, 50, 57-59, 61, 63, 66, 68-70, 72-78, 80, 83-91, and 93-98 or, in other words, claims 40, 45, 50, 57-59, 61, 63, 66, 68-70, 72-78, 80, 83-91, and 93-98 are anticipated by claims 1-11, 17, 21, 23, and

44-60 of U.S. Patent No. 6,326,166. Specifically, the methods of claims 1-11, 17, 21, 23, and 44-60 of '166 are drawn to the same nucleic acids and methods for modulating expression of a gene in a cell as instant claims 40, 45, 50, 57-59, 61, 63, 66, 68-70, 72-78, 80, 83-91, and 93-98, but the claims of 1-11, 17, 21, 23, and 44-60 of '166 are limited to nucleic acids encoding a chimeric protein that comprises a composite nucleic acid-binding domain, which composite domain comprises at least two nucleic acid binding domains not present together as such in nature. The nucleic acids and methods are also further limited to containing an additional separate domain, such as a ligand binding domain. This anticipates the instantly claimed method not limited to non-naturally occurring composite nucleic acid-binding domain and not limited to further comprising a separate ligand binding domain.

Conclusion

No claims are allowed.

Certain papers related to this application may be submitted to Art Unit 1636 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). The official fax telephone numbers for the Group are (703) 308-4242 and (703) 305-3014. NOTE: If Applicant does submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning missing attachments or other minor formalities of this communication should be directed to the patent analyst, Zeta Adams, whose telephone number is (703) 305-3291.

Any inquiry concerning rejections or other major issues in this communication or earlier communications from the examiner should be directed to Terry A. McKelvey whose telephone number is (703) 305-7213. The examiner can normally be reached on Monday through Friday, except for Wednesdays, from about 7:30 AM to about 6:00 PM. A phone message left at this number will be responded to as soon as possible (i.e., shortly after the examiner returns to his office).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Remy Yucel, can be reached at (703) 305-1998.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Terry A. McKelvey
Terry A. McKelvey, Ph.D.
Primary Examiner
Art Unit 1636

September 30, 2002